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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/529,722	04/19/2000	DAVID J SQUIRRELL	124-765	3335

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/529,722	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 January 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *02 January 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *58-66*.

   Claim(s) withdrawn from consideration: *NONE*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

David J. Steadman

ADVISORY ACTION

1. Claims 58-66 are pending in the application.

2. Claims 58-66 stand finally rejected.

3. Cancellation of claims 47-57 and addition of claims 58-66 in Paper No. 25, filed 01/02/02, is acknowledged and has been entered into the record.

4. The request for reconsideration has been considered but does not place the claims in condition for allowance for the reasons described below.

5. The written description rejection of claims 58-66 under 35 U.S.C. 112, first paragraph, is maintained. Applicants remark (page 4 of Paper No. 25) that the examiner has indicated in the Office action of Paper No. 22 that "amending claims 47 and 55 to include the details of claims 49 and 57, respectively, 'would appear' to overcome the Section 112, first paragraph, 'written description' rejection of claims 47-57". It is noted that this is a misrepresentation of the examiner's statement. Instead, the examiner stated, "It is noted that the limitations of claims 49 and 57, if incorporated into claims 47 and 55, respectively, would appear to *provide sufficient written description of a nucleic acid encoding a mutant AK enzyme*" (Paper No. 22, page 3, lines 2-4; italics added for emphasis). As applicants have correctly noted, the examiner should have indicated that the limitation of claim 57 should be incorporated into claim 50 and not claim 55. The recited genus of nucleic acids encoding the mutant AK polypeptide of claims 58 and 60 are adequately described in the specification as the claims recite both function, i.e., encoding a polypeptide having adenylate kinase activity, and structure, i.e., mutations at positions 87 or 107 of the amino acid sequence of E. coli AK. It is noted that at the time of the invention, the amino acid sequence of E. coli AK and encoding nucleic acid were well known to a skilled artisan as cited in the specification as being disclosed by Witinghofer (*Nucleic Acids Res* 13:7139-7150) and Liang et al. (*Gene* 80:21-28) at page 5, lines 2-4. Therefore, one of skill in the art would recognize that applicants were in possession of the recited genus of nucleic acids encoding mutant E. coli AK polypeptides at the time of the invention. However, as stated in previous Office actions, the specification has not provided adequate written description for the genus of nucleic acids encoding luciferase polypeptides that retain at least

partial activity at temperatures of 37 degrees Celsius or more. While the function of the genus of nucleic acids is recited in the claim, as stated in previous Office actions, the court in *UC California v. Eli Lilly*, (43 USPQ2d 1398), established that claims to genetic material cannot be described solely by their functional features as is the instant case. Thus, the rejection of claims 58-66 is maintained for the reasons discussed above and for the reasons of record.

6. The scope of enablement rejection of claims 58-66 under 35 U.S.C. 112, first paragraph, is maintained. Applicants argue (beginning at page 5 of Paper No. 25) the amendment to the claims obviates the scope of enablement rejection. Applicants quote lines 13-17 at page of Paper No. 22 wherein the examiner provides an indication of enabled subject matter. Applicants' arguments are not found persuasive. Upon further consideration of the scope of enablement rejection, it is the examiner's position that applicants have failed to enable a nucleic acid encoding all luciferase polypeptides that retain at least partial activity at temperatures of 37 degrees Celsius *or more* (italics added for emphasis). The specification provides insufficient guidance for enabling the entire scope of recited nucleic acids encoding thermostable luciferase polypeptides. The only guidance in the specification directed to a nucleic acid encoding a thermostable luciferase is cited as being disclosed in European Patent Application 92110808.0 or WO95/25798 (see page 8, lines 19-22 of the instant specification). While review of WO95/25798 indicates that the disclosed luciferase enzymes are stable at 37 degrees Celsius, there is no indication that these enzymes are stable at *any* temperature greater than 37 degrees Celsius. Furthermore, one of skill in the art would recognize that such enzymes would not be active at *any* temperature greater than 37 degrees Celsius. There is no guidance provided in the specification or the prior art for making a nucleic acid encoding a luciferase that is active at *any* temperature greater than 37 degrees Celsius and one of skill in the art would recognize the high degree of unpredictability and experimentation that would be required to make such nucleic acids. Thus, the specification has not provided enablement for all nucleic acids encoding luciferase polypeptides that are active at *any* temperature greater than 37 degrees Celsius.

7. The rejection of claims 58-66 under 35 U.S.C. 103(a) as being unpatentable over EP 373962 in view of Belinga et al. (J Chromat A 695:33-40), Gilles (Proc Natl Acad Sci, USA 83:5798-5802), and Kajiyama et al. (Biochemistry 32:13795-13799) is maintained. Applicants argue (beginning at page 5 of Paper No. 25) EP 373962 teaches the production of thermostable enzymes, which have very high thermostability. Applicants argue that because the thermostable enzyme of EP 373962 is very thermostable, there is no difficulty in the inactivation of thermolabile contaminants. Applicants argue that the method of EP 373962 uses temperatures in excess of 70 degrees Celsius. Applicants argue that an ordinarily skilled artisan attempting to produce a protein that is not thermostable in the sense intended by EP 373962 would not consider this reference to be applicable. Applicants argue that, while Kajiyama et al. teach a thermostable luciferase, the thermostable luciferase of Kajiyama et al. would not be considered thermostable in the context of EP 373962. Applicants argue that the thermostable luciferase of Kajiyama et al. is completely inactivated at temperatures greater than 65 degrees Celsius. Applicants argue the cited references provide no teaching or suggestion for relatively low temperature inactivation of contaminants such as is provided by the instant invention. Applicants conclude that the combination of cited references fails to teach or suggest the claimed invention. Applicants' arguments are not found persuasive. As is clear from applicants' arguments, the term "thermostable" is a relative term. Whether the enzyme of Kajiyama et al. would have been considered "thermostable" to the extent used in EP 373962 is not at issue. Clearly the temperatures used in the Examples provided in EP373962 (typically between 70 and 80 degrees Celsius) would have inactivated the thermostable luciferase of Kajiyama et al. As such, one of ordinary skill in the art would not have applied such extreme temperatures to the luciferase of Kajiyama. Instead, the reference of EP 373962 was cited in order to demonstrate that methods of inactivating contaminant proteins from a relatively thermostable protein were known in the art at the time of the invention. EP 373962 teaches a method for obtaining a thermostable enzyme free from unwanted contaminants by: providing a mesophilic host cell engineered to express a gene encoding heterologous thermostable enzyme, culturing said mesophilic cell to produce said thermostable enzyme, and heating a mixture comprising said unwanted contaminant to inactivate the unwanted contaminant at

a termperature not sufficient to inactivate the thermostable enzyme (column 2, lines 21-37). Kajiyama et al. teach their thermostable luciferase is stable at temperatures up to 50 degrees Celsius (Figures 2, 3, and 5; 50 degrees Celsius was the highest temperature used in the determination). Gilles teaches E. coli strain CR341 T28, which endogenously expresses a thermolabile AK polypeptide. Following the method of EP 373962, one would have transformed E. coli strain CR341 T28 with the expression vector of Kajiyama encoding the thermostable luciferase, expressed the thermostable luciferase, and treated with heat in order to denature the mutant AK. One would have been motivated to do so because of the teaching of Belinga who teaches the necessity of removing adenylate kinase from luciferase (page 33, left column). The cited references teach all limitations of the claims, provide a reasonable expectation of success, and provide motivation for practicing the invention. As such, the cited references make obvious claims 58-66.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

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